A New Model for Diurnal Blood Pressure Profiling

Square Wave Fit Compared With Conventional Methods

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For the characterization of diurnal blood pressure variation, we developed a simple mathematical model that nevertheless does justice to the specific form characteristics of individual blood pressure registrations. Analysis was based on 24-hour continuous intra-arterial measurement of blood pressure obtained in 23 hospitalized patients with mild-to-moderate untreated essential hypertension (mean±SD, 112±13 mm Hg). The day-night difference for mean arterial pressure varied markedly (mean, 18.6 mm Hg; range, 6.8–36.0). Inspection of profiles suggested a model of blood pressure as two contiguous, complementary periods of constant pressure, a so-called square wave. Determination of the times of transience between both periods (segmentation) was performed individually using a least-square error criterion. Results were compared with those obtained by conventional methods, including analysis by Fourier modeling. The square wave fit accounted for a larger fraction (66%) of circadian variance of mean arterial pressure than modeling based on segmentation by visual inspection (59%, considerable observer bias) or by clock time (50%). Application of the Minnesota Cosinor Method resulted in the poorest description (47%). Segmentation based on harmonic modeling (61%) appeared to be cumbersome (10 harmonics needed), and the significance of additional information offered over the square wave fit is dubious. Observer bias makes segmentation by visual inspection unsuitable for assessment of the circadian variance of blood pressure. Even when daily activities are strictly regulated (hospital environment), circadian variance is not well modeled by clock time. As compared with harmonic analysis, square wave fitting is simple, and it appears to best model the circadian variance. The method can also be applied to data obtained from noninvasive ambulatory blood pressure monitoring. (Hypertension 1992;19:595–605)

Key Words • ambulatory blood pressure monitoring • blood pressure • circadian rhythm

Blood pressure tends to be highest in the morning, decreasing gradually during the day to reach its lowest values at night. The actual blood pressure pattern found is strongly influenced by factors like the amount of physical activity and periods of rest. Nevertheless, a constant and prominent feature in normotensive men is a fall of blood pressure during the night, which constitutes a major fraction of the total diurnal blood pressure variation. The question as to whether there is an internal biological "blood pressure clock" analogous to the one responsible for the circadian variation of certain hormone levels and body temperature is still open. Various pathologies have been shown to alter circadian blood pressure fluctuations. For instance, a paradoxical rise in blood pressure at night was found in patients with sleep apnea syndrome, 4 preeclamptic toxemia, 5 and autonomic neuropathy. 6 A more or less constant 24-hour blood pressure level was observed in patients with malignant hypertension, 7 pheochromocytoma, 8 and Cushing's syndrome. 9 Also, after heart transplantation an abnormal circadian blood pressure profile has been described. 10 Since in these patients it appeared to be very difficult to unravel the quantitative effect of various intrinsic and extrinsic factors on blood pressure level, there is a considerable interest in an objective quantitative description of the circadian blood pressure variation.

In most analyses, characterization of 24-hour blood pressure was based on averaging records at fixed clock times or, slightly better, after synchronizing records relative to the time of waking. These procedures segment the profile into a high-pressure period, roughly corresponding to the day, and a low-pressure period corresponding to the night. The difference in mean blood pressure value over the two periods then corresponds to circadian variation.

Obviously, proper and objective description of 24-hour blood pressure variation is served by a mathematical model. The Minnesota Cosinor method, 11 which has been used most often, is probably one of the least accurate methods, since the basic assumption that the high- and low-pressure periods have the same length is...
incorrect and violates the reality of the diurnal life cycle. Nowadays, most investigators agree that the reported sinusoidal pattern of blood pressure variation probably is an artifact caused by averaging individual records without synchronization for such variables as time of sleep, time of waking, or type of activity. An alternative approach is Fourier analysis, a technique by which the individual 24-hour blood pressure profile is modeled as a superposition of cosine functions. Recently, in a report describing blood pressure profiles of shift workers, Chau et al. \(^{12}\) reported such a method. By statistical analysis of their 24-hour blood pressure data, they found that four harmonics were needed to model the profile. However, when more harmonics have to be used, as will be shown to be the case in our material, the interpretation of the synthesized signal, and therefore the determination of blood pressure shifts, is rather cumbersome.

In the present study, we describe a new mathematical model for the characterization of 24-hour blood pressure profiles. This model describes the profile as a square wave with exactly one period of high pressure and one period of low pressure. The duration of the two periods is only constrained by the requirement that their sum equals 24 hours. We applied this model to a collection of 23 recordings of 24-hour intra-arterial blood pressure measurement and compared the results with those obtained by other methods.

### Methods

#### Subjects and Blood Pressure Measurements

In a group of 23 male subjects with moderate essential hypertension (mean±SD of 24-hour mean arterial pressure, 112±13 mm Hg; range, 86–138 mm Hg), blood pressure was recorded continuously for a period of 24 hours. All patients gave informed consent to undergo intra-arterial measurements, which were approved previously by the Ethical Committee of the Dijkzigt Hospital. None of the subjects had received medication for hypertension for at least 3 weeks. All subjects were otherwise healthy. During blood pressure registrations, patients were hospitalized, but were not restricted in their activities.

Blood pressure registrations were obtained by means of the Oxford technique\(^{13}\) by which blood pressure is continuously measured via a catheter in the brachial artery and is recorded on an Oxford Medilog II recorder (Oxford Medical Systems, Oxon, England). The catheter is permanently flushed with a heparin solution to prevent clotting. Recorder, transducer, and perfusion unit are worn at heart level, which allows free movement of the patient.

#### Preprocessing of the Blood Pressure Signal

Blood pressure registrations were replayed and read into an Olivetti XP/7 computer system (Olivetti, Ivrea, Italy) with a sampling frequency of 160 Hz. For this procedure an AT-Codas AD-converter (Dataq Instruments, Akron, Ohio) with an accuracy of 12 bits was used. Subsequently, the blood pressure signal was analyzed by a computer program, which calculated systolic pressure, diastolic pressure, mean arterial pressure, and pulse interval of each beat.

A 24-hour blood pressure registration consists of about 100,000 heartbeats. Such a large number is rather impractical for analysis. Moreover, the data contain short-term fluctuations, e.g., the respiratory blood pressure variation. These fluctuations are evidently not to be considered as a part of the circadian variation, and their effect should be excluded when various models of circadian variation are compared quantitatively. For these reasons, we calculated 20-minute averages of blood pressure and heart rate values and used these values as input for further analysis. A time period of 20 minutes was chosen to attain a substantial data reduction while preserving the form characteristics of the circadian blood pressure variation, as was judged by visual inspection. The use of averages does not bias the 24-hour mean value of blood pressure and the parameters of the various models of circadian variation, while considerably reducing the effect of short-term fluctuations.

#### Blood Pressure Modeling

For analysis of the 24-hour blood pressure profiles, a new model was developed and applied. The method based on this model, i.e., fitting a square wave to each individual profile, is outlined in detail below. Results were compared with existing methods such as segmentation based on visual inspection of records by two independent observers, segmentation by clock time, the Cosinor Method, and Fourier modeling as reported by Chau et al. \(^{12}\) Since these methods have been described in detail elsewhere, they are summarized only in the “Appendix.” The method introduced by Chau, however, will be discussed in detail, since as part of the present research, its applicability was carefully analyzed.

The square wave fitting method. Figure 1 shows a 24-hour profile of mean arterial pressure, being a...
by square wave fitting and by harmonic analysis, can be assessed as follows. Of each blood pressure profile, mean and standard deviation of 20-minute periods were substituted. For these periods, except that their sum equal 24 hours. As a first step, both the blood pressure profile and each square wave are standardized to a mean of zero and a standard deviation of 1.0. The purpose of this scaling operation is to standardize outcomes of the cross correlation values to a range from 1.0 to -1.0. A value of 1.0 corresponds to a perfect fit, whereas a value of -1.0 corresponds to the worst possible fit. Subsequently, for each square wave the cross correlation value is calculated as the average product of the 72 corresponding values of the square wave and the blood pressure profile. The maximum among the \( N(N-1) \) values obtained in this way, \( c_{max} \), identifies the best-fitting square wave. This square wave is used to segment the original blood pressure profile in a high and a low pressure period. The fit resulting from this procedure is optimal with respect to the square error. The squared value of \( c_{max} \) expresses the fraction of total variation of the 24-hour blood pressure profile accounted for by the model. The percentage of total 24-hour variability (PVA) accounted for by the fitted square wave may therefore be expressed as

\[
PVA = 100 \times c_{max}^2
\]

The square wave model is characterized by a set of four parameters: \( t_{up} \), time point of passage of blood pressure from the low to the high pressure period; \( t_{down} \), time point of passage of blood pressure from the high to the low pressure period; \( BP_{up} \), observed mean blood pressure during the high pressure period; \( BP_{down} \), observed mean blood pressure during the low pressure period. These parameters are illustrated in Figure 1. Other parameters may be calculated from these: \( BP_{max} \), 24-hour mean pressure; \( BP_{up} - BP_{down} \), difference of mean observed blood pressure during the high and low pressure period. The circadian variation around \( BP_{max} \) is characterized by three parameters: \( BP_{up} - BP_{down} \), \( t_{up} \), and \( t_{down} \).

Since time of day is periodic, a circular representation, comparable to the cosinor display technique, can be used. In such a representation, a square wave is characterized by two vectors, \( U \) and \( D \), originating from the midpoint of a circle. The angles of the vectors with the vertical direction correspond to \( t_{up} \) and \( t_{down} \) respectively, whereas their lengths correspond to \( BP_{up} \) and \( BP_{down} \). These two vectors define a circular representation of a square wave, as is demonstrated in Figure 2A. For a sample of square waves, a confidence ellipse for the mean vectors \( U_{mean} \) and \( D_{mean} \) may be calculated assuming a bivariate normal distribution.

The square wave model assumes a bimodal distribution of 24-hour blood pressure. To establish whether such a distribution could be demonstrated in our subjects, a group histogram of 24-hour blood pressure was constructed after standardization of the individual profiles to the same mean and standard deviation. For these two parameters, the group averages of mean and standard deviation in individual profiles were substituted.

Most studies on circadian blood pressure variation are based on cuff measurements. The use of incidental measurements, however, has a detrimental effect on the precision, and in some cases, on the accuracy of model parameter estimation. To assess the sensitivity of the square wave fit to these effects, 200 profiles consisting of incidental measurements were simulated for each subject as follows. Of each blood pressure profile, mean and standard deviation of 20-minute periods were known. Single measurements for each period were generated by drawing at random from the normal distributions defined by these parameters, a so-called Monte Carlo experiment. Square wave parameters obtained from these 200 profiles were compared with values obtained from the corresponding profile consisting of continuous measurements. Mean and standard deviation of these differences were calculated in each individual, and subsequently averaged over the group. These parameters indicate the inaccuracy and imprecision, respectively, that are introduced by the use of incidental measurements for the average subject. Also, the standard deviation of the mean difference over the group was determined over the 200 experiments. This parameter indicates the imprecision in the group mean.

Comparison to conventional methods: Obviously, segmentation of 24-hour blood pressure in two periods is a simplification of reality, and therefore a patent "truth," by which the methods can be verified, does not exist. However, the plausibility of the times of transience between the high and low pressure period, as obtained by square wave fitting and by harmonic analysis, can be assessed by a comparison with the results of visual inspection. We assumed that if two observers agreed...
FIGURE 2. Representation of square wave parameters of a 24-hour blood pressure profile with a modeled high and low pressure span of 115 mm Hg and 75 mm Hg, respectively, and a time of passage to the high and low pressure period of 7 AM and 11 PM, respectively. The two vectors (U and D) define a circular representation of the modeled blood pressure profile (virtual data, panel A). Mean vectors from our patient group and corresponding 95% confidence intervals are shown in panel B. BP$_{\text{high}}$, observed mean blood pressure during the high pressure period; BP$_{\text{low}}$, observed mean blood pressure during the low pressure period; t$_{\text{up}}$, time point of passage of blood pressure from the low to the high pressure period; t$_{\text{down}}$, time point of passage of blood pressure from the high to the low pressure period.

about a value for t$_{\text{up}}$ or t$_{\text{down}}$, this was a plausible time of transience. However, since we used 20-minute averages of blood pressure, a difference of 20 minutes between results should be allowed, and in such a case both values were considered to be plausible transience times. In all other cases, it was assumed that there was no single evident value for the time of transience. In these cases, plausibility of t$_{\text{up}}$ or t$_{\text{down}}$ could not be verified, and the recordings were excluded from the comparison.

We used the remaining values to determine whether the results of the various models were biased. For this purpose, we compared model values of t$_{\text{up}}$ and t$_{\text{down}}$ to average observer results. Significance of a tendency toward “later” or “earlier” values was tested two-sided at a probability level of 0.05 (sign test with ties10). The bias was assessed quantitatively by calculating the mean and standard deviation of the differences.

Another method to compare the appropriateness of the various models is based on comparing the percentage of total variance in 24-hour blood pressure profiles that is characterized by each model (PVA); for the square wave fit, it was calculated directly from c$. For the other models it was calculated according to its definition

\[
\text{PVA} = 100 \times \frac{\text{Variance}_{\text{model}}}{\text{Variance}_{\text{actual}}}
\]

A model that uses more characteristics can be expected to explain more of circadian variation than a model that uses fewer parameters. When models are compared in this way, the number of parameters that a model uses must therefore be taken into account.

**Results**

**Visual Inspection**

The time points of transience from the low to the high pressure period as determined by both observers show a good correspondence (Figure 3). In three cases, observer 2 indicated these points of transience earlier than observer 1, and in none of the cases later (not significant). In only one case was this difference more than one 20-minute period. On the average, the difference between observers is very small, having a mean value±SD of 0:07±0:25 hours. For t$_{\text{down}}$, however, this correspondence is worse. In 12 cases, observer 2 indicated a later value for t$_{\text{down}}$ than observer 1, and in three cases an earlier value. This indicates a bias of observer 2 toward later values for t$_{\text{down}}$ ($p<0.05$). For eight values, this difference is more than 20 minutes. For all 23 subjects, the mean value±SD of the difference is 0:29±1:09 hours.

Only the cases in which observers differed no more than 20 minutes about the transience times were used to test the plausibility of square wave and Fourier modeling outcomes. This reduces the number of values available to 22 for t$_{\text{up}}$ and to 15 for t$_{\text{down}}$. 

![Figure 3](http://hyper.ahajournals.org/)

*Scatterplots show comparison of t$_{\text{up}}$ (left panel) and t$_{\text{down}}$ (right panel) as indicated by two independent observers. Dashed line is the line of identity. Overlapping values are slightly shifted.*
Idema et al  Square Wave Profiling of 24-Hour Blood Pressure  599

Table 1. Results of Square Wave Fitting to Individual Profiles of Mean Arterial Blood Pressure

<table>
<thead>
<tr>
<th>Subject</th>
<th>t&lt;sub&gt;up&lt;/sub&gt;</th>
<th>t&lt;sub&gt;down&lt;/sub&gt;</th>
<th>t&lt;sub&gt;up&lt;/sub&gt;-t&lt;sub&gt;down&lt;/sub&gt;</th>
<th>BP&lt;sub&gt;up&lt;/sub&gt; (mm Hg)</th>
<th>BP&lt;sub&gt;down&lt;/sub&gt; (mm Hg)</th>
<th>BP&lt;sub&gt;up&lt;/sub&gt;-BP&lt;sub&gt;down&lt;/sub&gt; (mm Hg)</th>
<th>BP&lt;sub&gt;mean&lt;/sub&gt; (mm Hg)</th>
<th>cc&lt;sub&gt;max&lt;/sub&gt;</th>
<th>PVA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8:00 AM</td>
<td>11:20 PM</td>
<td>3:20 AM</td>
<td>109.24</td>
<td>93.10</td>
<td>16.14</td>
<td>103.41</td>
<td>0.75</td>
<td>56.4</td>
</tr>
<tr>
<td>2</td>
<td>7:00 AM</td>
<td>12:20 AM</td>
<td>5:20 AM</td>
<td>110.15</td>
<td>81.53</td>
<td>28.61</td>
<td>100.03</td>
<td>0.87</td>
<td>75.3</td>
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<td>3</td>
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<td>10:20 PM</td>
<td>2:00 AM</td>
<td>94.08</td>
<td>83.21</td>
<td>10.87</td>
<td>89.55</td>
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<td>64.4</td>
</tr>
<tr>
<td>4</td>
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<td>11:20 PM</td>
<td>3:00 AM</td>
<td>109.95</td>
<td>92.67</td>
<td>17.28</td>
<td>103.47</td>
<td>0.83</td>
<td>68.6</td>
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<tr>
<td>5</td>
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<td>11:20 PM</td>
<td>5:00 AM</td>
<td>143.51</td>
<td>124.29</td>
<td>19.21</td>
<td>137.90</td>
<td>0.79</td>
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</tr>
<tr>
<td>6</td>
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<td>9:20 PM</td>
<td>2:00 AM</td>
<td>139.46</td>
<td>127.46</td>
<td>12.00</td>
<td>134.29</td>
<td>0.72</td>
<td>51.7</td>
</tr>
<tr>
<td>7</td>
<td>6:20 AM</td>
<td>10:40 PM</td>
<td>4:00 AM</td>
<td>125.91</td>
<td>93.14</td>
<td>32.77</td>
<td>115.44</td>
<td>0.94</td>
<td>88.4</td>
</tr>
<tr>
<td>8</td>
<td>6:40 AM</td>
<td>7:40 AM</td>
<td>1:00 AM</td>
<td>129.13</td>
<td>105.91</td>
<td>23.22</td>
<td>118.49</td>
<td>0.86</td>
<td>74.5</td>
</tr>
<tr>
<td>9</td>
<td>6:00 AM</td>
<td>11:40 PM</td>
<td>5:00 AM</td>
<td>131.73</td>
<td>99.31</td>
<td>32.42</td>
<td>123.18</td>
<td>0.78</td>
<td>62.9</td>
</tr>
<tr>
<td>10</td>
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<td>8:00 PM</td>
<td>2:00 AM</td>
<td>116.60</td>
<td>91.29</td>
<td>25.31</td>
<td>106.41</td>
<td>0.89</td>
<td>78.5</td>
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<td>11</td>
<td>5:40 AM</td>
<td>12:20 AM</td>
<td>6:00 AM</td>
<td>131.72</td>
<td>121.47</td>
<td>10.25</td>
<td>129.45</td>
<td>0.46</td>
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<td>12:20 AM</td>
<td>6:00 AM</td>
<td>119.31</td>
<td>95.80</td>
<td>23.52</td>
<td>113.11</td>
<td>0.90</td>
<td>80.6</td>
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<tr>
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<td>11:20 PM</td>
<td>5:00 AM</td>
<td>106.25</td>
<td>88.84</td>
<td>17.41</td>
<td>100.93</td>
<td>0.79</td>
<td>62.7</td>
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<td>6:00 AM</td>
<td>8:00 PM</td>
<td>2:00 AM</td>
<td>124.40</td>
<td>104.96</td>
<td>19.44</td>
<td>116.30</td>
<td>0.80</td>
<td>64.6</td>
</tr>
<tr>
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<td>6:00 AM</td>
<td>8:00 PM</td>
<td>2:00 AM</td>
<td>119.21</td>
<td>91.40</td>
<td>27.80</td>
<td>107.62</td>
<td>0.88</td>
<td>76.6</td>
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<td>7:20 AM</td>
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<td>91.18</td>
<td>16.73</td>
<td>102.79</td>
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<tr>
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<td>9:40 PM</td>
<td>noon</td>
<td>104.53</td>
<td>93.10</td>
<td>11.44</td>
<td>98.82</td>
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<tr>
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<td>7:30 PM</td>
<td>1:30 PM</td>
<td>131.84</td>
<td>109.86</td>
<td>21.98</td>
<td>119.63</td>
<td>0.87</td>
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</tr>
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<td>19</td>
<td>6:40 AM</td>
<td>12:20 AM</td>
<td>6:00 AM</td>
<td>117.53</td>
<td>90.46</td>
<td>27.07</td>
<td>110.39</td>
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<tr>
<td>20</td>
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<td>11:40 PM</td>
<td>7:20 AM</td>
<td>130.33</td>
<td>92.22</td>
<td>38.11</td>
<td>118.68</td>
<td>0.94</td>
<td>88.2</td>
</tr>
<tr>
<td>21</td>
<td>8:20 AM</td>
<td>12:20 AM</td>
<td>4:00 AM</td>
<td>89.54</td>
<td>78.59</td>
<td>10.96</td>
<td>85.89</td>
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<td>48.3</td>
</tr>
<tr>
<td>22</td>
<td>7:40 AM</td>
<td>11:40 PM</td>
<td>4:00 AM</td>
<td>130.61</td>
<td>100.56</td>
<td>30.05</td>
<td>120.59</td>
<td>0.88</td>
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</tr>
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<td>23</td>
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<td>11:00 PM</td>
<td>5:00 AM</td>
<td>121.86</td>
<td>91.16</td>
<td>30.71</td>
<td>112.48</td>
<td>0.89</td>
<td>79.9</td>
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</table>

Mean 7:05 AM 10:37 PM 2:29 AM 119.21 97.46 21.75 111.69 0.81 66.1
SD 1:04 1:43 2:01 13.93 12.95 8.05 13.06 0.11 16.2

BP<sub>mean</sub>, average 24-hour mean arterial pressure; BP<sub>up</sub> and BP<sub>down</sub>, average mean arterial pressure observed during the high and low pressure periods, respectively; t<sub>up</sub> and t<sub>down</sub>, times of transience to the high and low pressure periods, respectively; cc<sub>max</sub>, cross correlation value of best fitting square wave; PVA, percentage of 24-hour variance modeled.

Square Wave Method

Table 1 displays results of square wave fitting of the blood pressure profile of the 23 subjects together with their mean and standard deviation. Of the values of t<sub>up</sub>, 90% are in the range 5:30 to 8:30 AM. The distribution of t<sub>down</sub> in this range seems uniform. Of the values of t<sub>down</sub>, 90% are in the range between 8 PM and 12:30 AM. The distribution of t<sub>down</sub> is skewed: most blood pressure profiles have a time of passage from the high to the low pressure span between 11 PM and midnight, but in some profiles this passage occurs 2-3 hours earlier; in none does this occur more than half an hour later. The distribution of cc<sub>max</sub> and PVA is also skewed. Low values of PVA and cc<sub>max</sub> seem to coincide with low values of BP<sub>up</sub>-BP<sub>down</sub>, but have no evident relation with t<sub>up</sub> or t<sub>down</sub>. Figure 2B is a graph representative of mean square wave parameters of our group.

We compared the values of t<sub>up</sub> and t<sub>down</sub> obtained by square wave fitting to corresponding values obtained by visual inspection (Figure 4A, Table 2). In 21 of 22 profiles, values of t<sub>up</sub> were similar. For t<sub>down</sub>, this was the case in 10 of 15 profiles, with a bias toward later values than observers. For both parameters, the mean difference with observer results was negligibly small, but for t<sub>down</sub> there was a considerable scatter.

The standardized group histogram of 24-hour blood pressure (Figure 5) clearly demonstrates a bimodal distribution of blood pressure in our patient group. About one third of the samples is contained in a small peak, which represents the distribution of pressures up to 104 mm Hg. This peak has a median value of approximately 96 mm Hg. About two thirds of the samples is contained in a larger peak, which has a median value of approximately 118 mm Hg. The median values in the distributions are similar to the average values of BP<sub>up</sub> and BP<sub>down</sub> as determined by square wave analysis; they are 97.4 and 119.2 mm Hg, respectively.

The sensitivity of square wave parameters to the use of incidental measurements is demonstrated in Table 3. The estimation of square wave parameters from incidental measurements is unbiased; the scatter in the estimation of individual and group parameters, however, is considerable.

Segmentation Based on Modeling With Multiple Harmonics

We determined the number of harmonics to be used in the Fourier model according to the two criteria that are described in the "Appendix." In Table 4, runs-test values for our sample of 23 subjects are demonstrated. For each number of harmonics, maximal, minimal, and mean values of z over the 23 subjects are given. In the column farthest to the right the number of cases with z outside the 95% prediction area is displayed. The table
FIGURE 4. Scatterplots show comparison of transience times as indicated by square wave modeling (panel A) and by harmonic analysis (panel B) to average results of visual inspection. Only times on which both observers agree within 20 minutes are included in the plot. In panel A, overlapping values are slightly shifted. $t_{huh}$ and $t_{low}$, time of transience to the high and low blood pressure period, respectively.

shows that, according to the first criterion, only a Fourier model with 10 or 11 harmonics is adequate. According to the second criterion, models with eight up to 12 harmonics are acceptable. This is in contrast to the study presented by Chau,12 in which, according to the second criterion, four or five harmonics were sufficient to model circadian blood pressure variation.

A possible explanation for this difference may be that we used 20-minute averages of blood pressure, whereas the original study by Chau was based on one single measurement in each period of comparable length. To validate this hypothesis, we simulated single measurements from our data by a Monte Carlo experiment and subsequently determined the number of harmonics needed in the model. This procedure was repeated 20 times. According to the first criterion, five harmonics (15 cases) or six harmonics (five cases) were needed. The second criterion required three (three cases), four (four cases), five (eight cases), or six (five cases) harmonics in the Fourier model. It may be concluded that

the use of single measurements instead of averages of continuous measurements reduces the number of harmonics that is needed for an adequate fit. This may be explained by the random variation between single blood pressure measurements that obscures systematic variation that remains from an inadequate fit. To establish the sensitivity of the method to the number of harmonics in the Fourier model, we proceeded with calculations using a model of four, eight, and 10 harmonics.

The average values for $t_{huh}$ and $t_{low}$ obtained by Fourier modeling are displayed in Table 5. A comparison with values obtained by visual inspection is given in Table 2. As expected, the plausibility of results of the four-harmonics model is poor, agreeing with observer results in only four of 22 cases for $t_{huh}$ and in three of 15 cases for $t_{low}$. Both parameters are biased in such a way that, on the average, the duration of the low pressure period is underestimated by more than 2 hours. Applying an eight-harmonics model gives a considerably larger number of plausible values, and the 10-harmonics model results in the largest number of plausible values for $t_{huh}$ and $t_{low}$ agreeing with observers in 12 of 22, and in eight of 15 cases, respectively (Figure 4B). For the 10-harmonics model, however, there is a tendency toward earlier values of $t_{huh}$ as compared with visual inspection ($p<0.05$). The number of plausible values obtained by any of the Fourier models is lower than the number obtained by square wave fitting. For $t_{huh}$, the

| Table 2. Comparison of Modeled Transience Times to Results of Visual Inspection |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| $t_{huh}$ ($n=22$)               |                                 | $t_{low}$ ($n=15$)               |                                 |
| Mean±SD of difference (hours)   | No. of differences (≤0:20 hours)| Mean±SD of difference (hours)   | No. of differences (≤0:20 hours)|
|                                 | Biased toward                   |                                 | Biased toward                   |
| Square wave model               | 0.06±0.35                      | 21                              | 0.01±1.26                      | 10                              |
|                                 |                                 | ...                             |                                 | Later values                    |
| Segmentation based on a four-harmonic Fourier model | -1.37±1.35                    | 4                               | 0.45±1.07                      | 3                               |
|                                 |                                 | Earlier values                  |                                 | Later values                    |
| Segmentation based on an eight-harmonic Fourier model | -0.12±0.54                    | 10                              | -0.04±1.30                     | 7                               |
|                                 |                                 | ...                             |                                 | ...                             |
| Segmentation based on a 10-harmonic Fourier model | -0.25±0.49                     | 12                              | -0.15±1.22                     | 8                               |
|                                 |                                 | Earlier values                  |                                 | ...                             |

A positive difference indicates later model values. Bias toward later or earlier values was calculated from the sign of the differences (sign test with ties, $p<0.05$). $t_{huh}$ and $t_{low}$, times of transience to the high and low pressure period, respectively.
scatter of the differences with visual inspection is larger for the Fourier models than for the square wave model, as it appears from the values of the standard deviation. For \( t_{\text{low}} \), the scatter is comparable.

Mean \pm SD of blood pressure gradients obtained by Fourier models using four, eight, and 10 harmonics over our group of 23 subjects were 7.4 ± 4.1, 16.5 ± 6.7, and 20.6 ± 9.2 mm Hg/hr for \( s_{\text{up}} \), and -7.5 ± 3.6, -17.8 ± 7.9, and -21.2 ± 7.6 mm Hg/hr for \( s_{\text{down}} \), respectively. Values obtained by the models with four and eight harmonics are smaller than those obtained by the model with 10 harmonics. Since the latter model provides a better fit to the original blood pressure profiles, we conclude that the four- and eight-harmonic models underestimate blood pressure gradients. The underestimation by the eight-harmonic model seems in conflict with the fact that adequacy of the fit has been established. Adequacy, though, is considered to be achieved if residuals of the fit of the entire 24-hour profile show no random positive or negative sequence. In periods of shorter duration, e.g., at the sides of the trough, there may still be a systematic pattern in the residuals.

Quantitative Comparison of Methods

We calculated the percentage of total 24-hour variability in individual profiles that the various models in this study accounted for. Mean and standard deviation of these values are displayed in Table 5, together with the number of parameters of each model. If appropriate, the mean values of \( t_{\text{up}} \) and \( t_{\text{low}} \), as determined by the method are also displayed in the two right columns.

### Discussion

**Visual Inspection**

The good correspondence between the two observers demonstrates that in most 24-hour registrations of heart rate and blood pressure, an evident and circumscribed transience to a period of higher activity is visible. In contrast to the small interobserver variation, there was a considerable scatter in the indicated times of transience between profiles, which indicates that even in the synchronizing hospital environment, activity patterns as they appear from the registrations may vary considerably. Apparently, segmentation based on clock time does not do justice to the interindividual variation in the circadian variance of blood pressure.

On the other hand, it is evident that in a considerable number of blood pressure profiles, there is no evident single value for \( t_{\text{low}} \). The observer bias for \( t_{\text{low}} \) that we have demonstrated will cause segmentation of blood pressure profiles by visual inspection to be observer dependent. Therefore, it cannot be used for a reproducible assessment of the circadian blood pressure variation. Similar problems can be expected for \( t_{\text{up}} \), when the rise of blood pressure in the morning is substantially reduced, as is the case in various pathological states that diminish the circadian variance. Since the characterization of circadian variance is of most interest in these cases, this is also an important limitation to the use of visual inspection.

**Square Wave Method**

Our comparison clearly indicates that models of circadian blood pressure variation based on segmentation of the profile in a contiguous high and low blood pressure span may cover a considerable fraction of total 24-hour blood pressure variance. In this respect, the models based on segmentation compare favorably with the Minnesota Cosinor Method. The model of segmentation is further supported by the bimodal distribution of blood pressure, which we demonstrated in this study. When the objective of blood pressure modeling is such a segmentation, the presented square wave fitting technique is optimal with respect to the square error. Moreover, since values for \( t_{\text{up}} \) and \( t_{\text{low}} \) are calculated to yield a best fit to a given profile, it is expected that the method yields valid results also when subject activities are not synchronized in time.

The time of passage to the high pressure span as determined by square wave fitting of mean arterial
pressure compared well with results obtained by visual inspection using clock time, heart rate, and blood pressure information. When observers agreed about the time of passage across the pressure span, square wave fitting resulted in a good or reasonable approximation of this time point. In many cases, however, there is apparently no evident single point in time for transience from the high to the low pressure span. Therefore, the interpretation of $t^\text{tr}$ as obtained by square wave fitting must be limited to its mathematical definition, i.e., the best fitting time of transience to the low blood pressure period. The method is conceptually simple, and its parameters are easy to interpret. Application of the method needs no human interpretation and therefore offers immediate and objective results.

In concordance with Di Rienzo et al., we found that the estimation of mean 24-hour blood pressure is highly sensitive to the use of incidental measurements. Also, the estimation of $t^\text{tr}$ and $t^\text{trans}$ by square wave fitting is unbiased. We conclude that the method can be applied in smaller data sets obtained in noninvasive ambulatory blood pressure measurements. An indication of the imprecision and accuracy of parameter estimation that results from the use of such material can be found in Table 3.

Clock Time

Surprisingly, modeling of circadian blood pressure variation by segmentation based on fixed clock time accounts for a large fraction of 24-hour variation when compared with the other, more sophisticated, methods in this study. Without fitting, more of circadian variation is described by the clock time model than by the cosinor model, even though the first model uses only one parameter, whereas the latter needs two parameters. Two causes are responsible for this good performance. First, the period of rest and the period of activity are synchronized in the subjects of our study. Second, since the subjects did not work during the blood pressure registration, blood pressure during the period of activity was relatively constant. Segmentation based on fixed clock times is easy to perform, and the interpretation of its parameter, i.e., the difference of mean observed blood pressure during the two time periods, is straightforward. However, the description of circadian varia-

### Table 5. Comparison of Models

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean±SD of PVA (%)</th>
<th>No. of Parameters</th>
<th>$t^\text{tr}$ (hours)</th>
<th>$t^\text{trans}$ (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Square wave</td>
<td>66±16</td>
<td>3</td>
<td>7:05 AM±1:04</td>
<td>10:37 PM±1:43</td>
</tr>
<tr>
<td>Observer 1</td>
<td>58±18</td>
<td>3</td>
<td>6:55 AM±0:53</td>
<td>10:52 PM±1:06</td>
</tr>
<tr>
<td>Observer 2</td>
<td>59±17</td>
<td>3</td>
<td>6:49 AM±0:53</td>
<td>11:21 PM±0:45</td>
</tr>
<tr>
<td>Clock time</td>
<td>50±18</td>
<td>1</td>
<td>(7:00 AM±0:00)</td>
<td>(11:00 PM±0:00)</td>
</tr>
<tr>
<td>Minnesota Cosinor Method</td>
<td>47±19</td>
<td>2</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Segmentation based on a ...</td>
<td>44±22</td>
<td>3</td>
<td>5:13 AM±1:40</td>
<td>12:10 AM±1:27</td>
</tr>
<tr>
<td>Segmentation based on an ...</td>
<td>60±18</td>
<td>3</td>
<td>6:38 AM±1:12</td>
<td>10:32 PM±1:41</td>
</tr>
<tr>
<td>Segmentation based on a ...</td>
<td>61±19</td>
<td>3</td>
<td>6:24 AM±0:54</td>
<td>10:14 PM±1:40</td>
</tr>
</tbody>
</table>

PVA, percent of 24-hour variance modeled; $t^\text{tr}$ and $t^\text{trans}$ times of transience to the high and low pressure period, respectively.

Apart from common hospital activities, like meals and the times of night rest, no synchronization of activities was forced on the subjects in our group. Some subjects showed a marked lowering of blood pressure during the early evening to a level that was comparable to levels during the night, probably as a consequence of relaxation, while others maintained a rather constant level of blood pressure until the beginning of the period of night rest. For $t^\text{tr}$, there was also a considerable scatter in the values. Modeling of blood pressure by fixed clock time periods cannot account for such differences.

**Minnesota Cosinor Method**

The Cosinor Method has been developed for the detection and quantification of biorhythms. When only the frequency of the rhythm is known, the use of a cosine is an obvious choice since harmonic analysis is a well-known tool of analysis of periodic phenomena and is theoretically well established. Also, it may well describe fluctuations that are sinusoidal, like the circadian fluctuation of adrenocorticotropic hormone level. Individual blood pressure profiles, however, do not have a sinusoidal shape; in particular, the duration of the low blood pressure period is in general shorter than the duration of the high period, and the morning rise of blood pressure is abrupt instead of gradual. However, many authors have used this method for the characterization of circadian blood pressure variation. The fact that, in spite of these drawbacks, this method has been reported to give acceptable results is caused by summation of blood pressure profiles in a group of recordings. Since the abrupt rise of blood pressure during the morning will be at slightly different times in the various recordings, the sum profile will show a faint, elongated rise of blood pressure that resembles the ascending side of a sine, but that is not a characteristic of individual blood pressure profiles. The cosinor method is therefore less appropriate to assess individual blood pressure profiles, and as expected, accounts for only a relatively small part of actual circadian blood pressure variation. This is not only caused by the use of fewer parameters than the models that characterize circadian variation by...
segmentation, since it performs less well than clock time, which uses only one parameter.

**Segmentation Based on Modeling With Multiple Harmonics**

Similar to the square wave fit, the method presented by Chau et al.\(^{12}\) segments 24-hour blood pressure in a high and a low pressure span and specifies the times of transience between these spans. This segmentation accounts for a percentage of total 24-hour variation that is nearly as high as square wave modeling, which is optimal in this respect. In addition to the square wave fit parameters, blood pressure gradients at the transience times are calculated.

Various factors influence the validity of these blood pressure gradients. First, their values depend on the number of harmonics in the model. The relevance of this number is stressed by the poor performance of the four-harmonic model applied to our data and by the different blood pressure gradient values obtained by the various models. This number is dependent on the number of measurements in the profile.\(^{14}\) Furthermore, it is dependent on the between-measurement variation, as we have demonstrated, and on the statistical criterion used to decide on this number. In our material, at least 10 harmonics were needed in the Fourier model. We could partially attribute the discrepancy to the use of single measurements in the former study, which introduces between-measurement variation. Furthermore, the subjects in the study by Chau et al.\(^{12}\) had 8-hour labor tasks during the registration. This may have caused a more sinusoidal form of individual blood pressure profiles, and such profiles may be described by fewer harmonics. As a consequence of the increased number of harmonics needed for the modeling of our material, a new criterion using visual identification of borders of the low pressure span was needed to determine times of transience between high and low pressure. This makes the procedure laborious and subjective.

Second, global criteria are used to decide on adequacy of the fit, whereas blood pressure gradients are a local property of the signal, for which the fit may not be adequate. If this is the case, estimation of the blood pressure gradients may be biased. For these reasons, blood pressure gradients obtained by this method are greatly influenced by the method of measurement and subsequent analysis, and it is not evident that the values presented so far are in fact mainly determined by the analyzed blood pressure profiles. The values should be interpreted with great care, and their use is limited by the incomparability between different measurement protocols. When estimation of blood pressure gradients is not among the purposes of blood pressure modeling, square wave fitting is a more objective and direct way of estimating \(t_{hp}, t_{lw}, \) \(BP_{hp},\) and \(BP_{lw}\), and is optimal with respect to the least square error of the fit.

An interesting finding of the present study is the discrepancy between \(t_{hp}\) as determined by visual inspection and square wave fitting on one hand and the Fourier model with 10 harmonics on the other hand. In a few cases, harmonic analysis resulted in values of \(t_{hp}\) that were 2–4 hours earlier than the values determined by observers or by square wave fitting. Since harmonic analysis indicates the largest gradient in the ascending track of blood pressure, we conclude that in these cases, the major part of the blood pressure rise is not at the time of the largest gradient, but occurs more gradually later in the morning. Since the gradient has been reported to be largest just after wakening, this suggests that segmentation based on the sleeping and wakening times is in some cases less appropriate for the modeling of circadian blood pressure variation.

The conclusions based on this current study are valid for hospitalized patients and probably hold for any population with a constant level of activity during the day. Additional research, however, is needed to assess the percentage of variation that the model accounts for in blood pressure profiles of outpatients.

**Appendix**

**Conventional Methods of Modeling**

**Visual inspection.** Two independent observers, who were familiar with blood pressure registrations but not acquainted with the square wave fitting method, were asked to divide the 24-hour registrations of mean arterial pressure in two complementary periods of activity and rest. For this segmentation, the combined information of clock time and 24-hour graphs of heart rate and systolic, diastolic, and mean arterial blood pressure was used. Subsequently, the average of mean arterial blood pressure observed during both periods was calculated. In this way, the 24-hour blood pressure profile was modeled as two periods of constant pressure. Values of \(t_{hp}\) and \(t_{lw}\) were compared to detect observer bias. For this purpose, the sign of the difference between both observers was tested for random distribution at a significance level of 95% (sign test with ties).\(^{16}\) Furthermore, mean value and standard deviation of the differences were calculated.

**Segmentation by Clock Time**

If the activity of a group of subjects is tightly coupled to the time of day, as is the case in a hospital environment, their activities will be synchronized rather strictly. In such a case clock time may be used to select periods of high and low blood pressure. We used the times of turning off the lights and of serving breakfast in the hospital (11 PM and 7 AM, respectively) to segment blood pressure profiles in two periods and modeled the 24-hour blood pressure profile using the average blood pressure during these two periods.

**Minnesota Cosinor Method (One Harmonic)**

This method enables the detection of a sinusoidal rhythm and the objective and quantitative determination of its amplitude and phase. It has been used by its authors\(^{12,19}\) and others\(^{20,21}\) to describe circadian blood pressure variation. Elaborate and critical reviews of the method are given by van Cauter and Huyberechts\(^{22}\) and Bingham et al.\(^{23}\) In short, the method fits a cosine with a period of 24 hours to a blood pressure profile. The phase of the fitted cosine is inverted and referred to as "acrophase." Amplitude and acrophase of the fitted cosine are subsequently used to describe circadian variation.

**Segmentation Based on a Multiple Harmonics Model**

The method described by Chau et al.\(^{12}\) quantifies the shape of a 24-hour blood pressure profile by Fourier modeling. The number of harmonics that is used in the model is determined by a statistical criterion. The modeled profile is not used to calculate circadian variance directly; instead, it is used to segment the original profile in a high and low pressure period. This procedure thus defines a set of parameters identical to
the square wave fit, which is used as characteristics of circadian blood pressure variation.

The segmentation is performed by identification of the minimum of the synthesized profile, followed by determination of the inflection points at both sides of this minimum (see Figure 6A for an example). These points are taken to be the points of transition between the periods of low and of high blood pressure. In addition, the slopes in the modeled blood pressure profile at these points are determined. These parameters indicate the maximum blood pressure gradients of the synthesized function and serve as additional characteristics of circadian variance. We will refer to them as $s_{up}$ and $s_{down}$ respectively. In this way, the method characterizes diurnal variation by a total of six parameters.

A fundamental part of the method is the determination of the number of harmonics needed for an adequate fit. Since the procedure for this determination is not explicitly described by Chau et al., it will be outlined here. A fit of a Fourier model to a single blood pressure profile is considered adequate if the distribution of positive and negative values of the residuals of the fit is random. To establish whether in a fit this criterion is fulfilled, the sequence of residuals in their chronological order is subdivided into alternating subsequences of positive and negative values. Such subsequences are called runs, and for such runs a statistical test can be applied to verify a null hypothesis of random distribution. In fact, the expectation value $E(r)$ of the number of runs and the corresponding standard deviation $S(r)$ under the null hypothesis are known. Thus, for a single fit yielding $R$ runs, the test statistic

$$z = \frac{R - E(r)}{S(r)}$$

may be defined. This statistic is approximately standard normally distributed under the null hypothesis. This implies that each profile has a probability smaller than or equal to 0.05 to produce a $z$ value outside the range $-1.96 < z < 1.96$. In the original study by Chau et al., the mean $z$ value ($z_{mean}$) and the number of $z$ values out of the reference range were used to decide adequacy of a Fourier model. According to their analysis, four harmonics were needed for an adequate fit of their blood pressure registrations. The exact criterion used for this decision, however, is not explained. For an objective comparison of our results to those obtained by Chau et al., an unambiguous definition of this criterion is required. For this purpose, we investigated two possible criteria.

When the $z$ values resulting from $n$ independent fits are considered to be a sample of $n$ elements from a standard normal distribution, it may be tested whether the mean value of $z$ found for $n$ fits is compatible with 0. The means calculated from a sample of $n$ follow a normal distribution with (in this case) 0 mean and a standard deviation of $1/\sqrt{n}$. Therefore, assuming a significance of 95%, harmonics should be added to the model until the mean value of $z$ is in the range from $-1.96/\sqrt{n}$ to $1.96/\sqrt{n}$.

The study of Chau et al. uses a sample size of forty-five 24-hour blood pressure registrations ($n=45$), corresponding to a 95% prediction range for $z_{mean}$ from $-0.292$ to 0.292. Using this criterion, none of the Fourier models presented in their study describe the systolic pressure adequately, and a model with five harmonics is adequate for diastolic pressure only. A different and more permissive criterion can be formulated using the probability levels of $z$ values resulting from individual fits. If the model is adequate, each profile has a probability smaller than or equal to 0.05 to produce a $z$ value outside the range $-1.96 < z < 1.96$. The 95% prediction interval for the maximum number of $z$ values out of this range in a sample of $n$ elements is subsequently calculated assuming a binomial distribution. From $n=45$ it follows that only Fourier models that result in four or fewer $z$ values out of the range $-1.96 < z < 1.96$ are acceptable at a significance level of 95%.

Figure 6. Modeling of circadian variation of blood pressure (dashed line) by harmonic analysis (continuous line), using four-, eight-, and 10-harmonic models. For the four-harmonic model (panel A), inflection points in the model nearest to the minimum pressure (□) define $t_{up}$ and $t_{down}$. This results in unrealistic values and a short modeled low pressure period. For the 8- and 10-harmonic models (panels B and C), a relevant subset of inflection points is selected visually (○). From these, inflection points with the largest blood pressure gradients (indicated by $s_{up}$ and $s_{down}$) define $t_{up}$ and $t_{down}$. $t_{up}$: time point of passage of blood pressure from the low to the high pressure period; $t_{down}$: time point of passage of blood pressure from the high to the low pressure period; $s_{up}$: modeled blood pressure gradient at $t_{up}$; $s_{down}$: modeled blood pressure gradient at $t_{down}$. 
For the data presented by Chau et al, this appears to be the case for both systolic and diastolic pressure if a Fourier model with five harmonics is used; a Fourier model with four harmonics is sufficient for diastolic pressure only. Since they concluded from their data that four harmonics offered an acceptable fit for both pressures, probably neither the first nor the second criterion has been used.

To establish the sensitivity of the method to the number of harmonics used, we performed calculations using a Fourier model with four harmonics as in the study by Chau et al; a model with 10 harmonics as is required by our first criterion; and a model with eight harmonics, which is sufficient according to the second criterion. The use of more than four harmonics, however, requires a modification of the original segmentation procedure. In the study by Chau et al, the limits of the low and high pressure spans correspond to the inflection points in the synthesized blood pressure profile nearest to the minimum pressure (Figure 6A). The addition of more harmonics to the model, however, increases the number of inflection points and therefore decreases their distance. As a consequence, a fit modeled by, for instance, eight harmonics produces low pressure spans with a duration of approximately 2 hours, which obviously is an unrealistic value. Therefore, we modified the algorithm of Chau et al as follows. Each 24-hour blood pressure profile in our sample included a large period of relatively low pressure, approximately during the period of rest. This period induced a minimum pressure in the modeled profile and a surrounding trough. The sides of this trough were identified visually. Some of these sides appeared short and steep and showed one inflection point, which was selected as a transition between the high and low pressure span. In some profiles, however, the transitions were gradual and elongated and contained two or three inflection points, as is illustrated in Figures 6B and 6C. In such cases, the inflection point with the largest blood pressure gradient was chosen. This modified algorithm was applied when more than four harmonics were used in the Fourier model.

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